REMARKS

This application is rejected under 35 U.S.C. § 112, first paragraph, for the reasons noted in the official action. The inadequate written description rejection is acknowledged and respectfully traversed in view of the following remarks.

Claims 60, 21, 73 and 74 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the reasons noted in the official action. The rejected claims are accordingly amended, by the above claim amendments, and the presently pending claims are now believed to particularly point out and distinctly claim the subject matter regarded as the invention, thereby overcoming all of the raised § 112, second paragraph, rejections. The entered claim amendments are directed solely at overcoming the raised indefiniteness rejections and are not directed at distinguishing the present invention from the art of record in this case.

Claims 58-72 and 75-86 are rejected, under 35 U.S.C. § 103(a), as being unpatentable over Barton et al. '586 in view of Lee et al. '653 The Applicant acknowledges and respectfully traverses the raised obviousness rejection in view of the following remarks.

It should be noted that present claims 59-86 are all dependent on claim 58. Therefore, if base claim 58 is inventive over the prior art, claims 59 to 86 should benefit from patentability of claim 58.

Claim 58 of the present application calls for "a nucleic acid oligomer modified by attaching a catalytically redox-active moiety, characterized in that the catalytically redox-active moiety is selected from the group consisting of native or modified alcohol dehydrogenase, native or moiety fructose dehydrogenase, native or modified lactate dehydrogenase, and native or modified peroxidases".

To sum up, independent claim 58 is directed to nucleic acid oligomers which are modified by attaching specific enzymes, i.e., by attaching alcohol dehydrogenase, fructose dehydrogenase, lactate dehydrogenase or a peroxidase.

Barton et al. '586 is concerned with methods for the detection of genetic point mutations in nucleic acid sequences and its application to a biosensor (column 5, line 66 to column 6,

line 1). According to Barton et al. '586, an intercalative, redox-active moiety is attached to immobilized DNA duplexes at different separations from an electrode and probed electrochemically in the presence or absence of a non-intercalative, redox-active moiety (Abstract). Interruptions in DNA-mediated electron-transfer caused by base-stacking perturbations are reflected in a difference in electrical current, charge and/or potential (Abstract).

In particular, Barton et al. '586 discloses electrodes modified with oligonucleotide duplexes combined with an intercalative, redox-active species (column 6, lines 2 to 5). The different methods for determining the presence of point mutations according to Barton et al. '586 all comprise at least the steps of contacting a first nucleic acid molecule with a second nucleic acid molecule under hybridizing conditions, wherein one of the nucleic acid molecules is derivatized with a functionalized linker, depositing this duplex onto an electrode, contacting the adsorbed duplex with an intercalative, redox-active moiety under conditions suitable to allow complex formation and measuring the amount of electrical current or charge generated (column 6, line 8 to column 7, line 26).

Therefore, all embodiments of the method disclosed by Barton et al. '586 require an intercalative, redox-active moiety. This is confirmed by the specification in column 7, lines 27 to 38 which reads:

> "The invention also relates to the nature of the redox-active moieties. The requirements of a suitable intercalative, redox-active moiety include the position of its redox potential with respect to the window within which the oligonucleotide-surface linkage is stable, as well as the synthetic feasibility of covalent attachment to the oligonucleotide. In addition, chemical and physical characteristics of the redox-active intercalator may promote its intercalation in a site-specific or a non-specific manner. In a preferred embodiment, the redox-active species is in itself an intercalator or a larger entity, such as a nucleic acid-binding protein, that contains an intercalative moiety."

Consequently, it is mandatory for the invention as disclosed by Barton et al. '586 to use a redox-active moiety which intercalates between the base-pairs of a double-stranded DNA

molecule. Only molecules showing specific properties are able to intercalate between DNA-base pairs. Such intercalators must have a Π-system occupied by electrons. Further, the intercalators must have a flat shape. The flat shape of the molecule is mandatory since the distance between two DNA-base pairs measures only 3.4 Å.

Barton et al. `586 teaches in column 13, lines 17 to 14:

> "An intercalator useful for the specified electrochemical assays is an agent or moiety capable of partial insertion between stacked base pairs in the nucleic acid double helix. Examples of well-known intercalators include, but are not limited to, phenanthridines (e.g., ethidium), phenothiazines (e.g., methylene blue), phenazines (e.g., phenazine methosulfate), acridines (e.g., quinacrine), anthraquinones (e.g., daunomycin) and metal complexes containing intercalating ligands (e.g., phi, chrysene, dppz)."

It should be noted that the enzymes specified in claim 58 of the present application, i.e., alcohol dehydrogenase, fructose dehydrogenase, lactate dehydrogenase and peroxidase do not exhibit the properties of an intercalator. The Applicant is providing the enclosed Figs. 1 and 2, schematically depicting the structure of alcohol dehydrogenase and lactate dehydrogenase. Both figures clearly show that the respective enzymes do not have a flat or even shape. Please note that fructose dehydrogenase and peroxidase exhibit similar structures.

On page 7 of the official action dated April 15, 2003, the Examiner states that Barton et al. `586 teaches nucleic acid oligomers modified by attaching redox proteins and enzymes which use prosthetic groups such as flavin or NAD.

This is not a correct interpretation of Barton et al. `586, since Barton et al. `586 use two different kinds of redox active moieties, one being attached to the DNA molecule is an intercalator as described above. The one not being attached to the DNA is a non-intercalative, redox-active species used for electrocatalysis (column 7, lines 39 to 42). This non-intercalative species is used to regenerate the intercalative redox-active species thereby allowing observation of catalytic currents (column 9, lines 29 to 34). Barton et al. `586 use the redox

proteins and enzymes cited by the Examiner as non-intercalative species. Therefore, these molecules are not attached to the DNA.

To sum up, Barton et al. '586 does not disclose or suggest a nucleic acid oligomer modified by attaching alcohol dehydrogenase, fructose dehydrogenase, lactate dehydrogenase or peroxidases as required by claim 58. It is submitted that a person skilled in the art would not come up with the idea to replace an intercalator as disclosed by Barton et al. '586 with an enzyme as specified by present claim 58 since the presence of an intercalator is mandatory to the invention of Barton et al. '586.

In the paragraph bridging pages 11 and 12 of the official action, the Examiner states that it would have been obvious to one having ordinary skill in the art to substitute and combine a structurally and functionally equivalent catalytic redox-active moiety of Lee et al. '653 in the modified nucleic oligomer of Barton et al. '586.

It is acknowledged that Lee at al. disclose alcohol dehydrogenase (column 5, lines 4/5), lactate dehydrogenase (column 5, line 4) and peroxidase (column 4, line 64) However, Lee et al. '653 does not teach to attach these enzymes to an oligonucleotide. Further more, as explained in detail above, a person skilled in the art would not use the enzymes disclosed by Lee et al. '653 in the modified nucleic acid oligomer of Barton et al. '586 due to the reasons mentioned above.

Lee et al. '653 discloses immobilization of enzymes and particularly immobilization of glucomylase and other enzymes on glass fibers (column 1, lines 6 to 8). The enzyme is embedded in a matrix coated on the exterior of the glass fibers (column 2, lines 37 to 39). The matrix is comprised of a polymer which has been insolubilized by cross-linking. The degree of cross-linking is controlled to permit penetration by the enzyme substrate which is to react with the enzyme (column 2, lines 39 to 43).

The cross-linking agents used by Lee et al. are bi-functional molecules. Preferred are dialdehydes containing 1 to 10 carbon atoms in addition to the carbon atoms in the aldehyde groups, especially dialdehydes containing 3 to 6 carbon atoms (column 5, lines 29 to 32).

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In addition, polyisocyanates are used, such as toluene diisocyanates, methylene bis(phenyl-4-isocyanate) and poly-phenylene-polymethylene polyisocyanates (column 5, lines 33 to 38).

Lee et al. '653 teaches to control the degree of cross-linking of the polyme by adjusting the amount of cross-linking agent applied (column 2, lines 48 to 50). The activity of the immobilized enzyme can be reduced excessively if too much cross-linking agent is applied. On the other hand, if the amount of cross-linking agent is too low, the enzyme's endurance is reduced (column 2, lines 50 to 59). The cross-linking agent may also link the enzyme to the polymer, thereby immobilizing it within the matrix (column 3, lines 44 to 47).

The preparation method of Lee et al. '653 results in a mixture of linked polymers, enzymes linked to polymers as well as enzymes linked to enzymes. This is no problem in the context of the teaching of Lee et al. '653, since it is the aim of Lee et al. '653 to determine the activity of the immobilized enzyme (column 6, lines 60 to 62). To achieve this goal, it is not necessary to know the exact structure of the polymers attached to the glass fibers. It is only important for Lee et al. '653 to attach as much enzymes as possible to the polymers, since the activity of the enzyme which is finally detected by Lee et al. does not depend on the structure of the polymer.

This is in contrast to the teaching of the present invention. On page 1 of the specification, it is disclosed that "the present invention is directed to a modified nucleic acid oligomer, as well as a method of electrochemically detecting sequence-specific nucleic acid oligomer hybridization events". The detection of sequence-specific nucleic acid oligomer hybridization events is only possible if the exact structure of the modified nucleic acid oligomers is known. Each oligonucleotide attached to an electrode has to be modified with at least one redox-active moiety. Without said redox-active moiety no current may be detected and consequently, no hybridization event may be detected. Therefore, a person skilled in the art would not apply the method of Lee et al. '653 to prepare a modified nucleic acid oligomer according to the present invention.

To sum up, none of the documents cited by the Examiner discloses or suggests a nucleic acid oligomer modified by attaching alcohol dehydrogenase, fructose dehydrogenase, lactate dehydrogenase and peroxidases as required by independent claim 58 of the present application. Therefore, the present application is novel and inventive over the prior art.

If any further amendment to this application is believed necessary to advance prosecution and place this case in allowable form, the Examiner is courteously solicited to contact the undersigned representative of the Applicant to discuss the same.

In view of the above amendments and remarks, it is respectfully submitted that all of the raised obviousness rejections should be withdrawn at this time. If the Examiner disagrees with the Applicant's view concerning the withdrawal of the outstanding rejections or applicability of the Barton '586 and Lee et al. 653 references, the Applicant respectfully requests the Examiner to indicate the specific passage or passages, or the drawing or drawings, which contain the necessary teaching, suggestion and/or disclosure required by case law. As such teaching, suggestion and/or disclosure is not present in the applied references, the raised rejection should be withdrawn at this time. Alternatively, if the Examiner is relying on his/her expertise in this field, the Applicant respectfully requests the Examiner to enter an affidavit substantiating the Examiner's position so that suitable contradictory evidence can be entered in this case by the Applicant.

In view of the foregoing, it is respectfully submitted that the raised rejections should be withdrawn and this application is now placed in a condition for allowance. Action to that end, in the form of an early Notice of Allowance, is courteously solicited by the Applicant at this time.

The Applicant respectfully requests that any outstanding objections or requirements, as to the form of this application, be held in abeyance until allowable subject matter is indicated for this case.

In the event that there are any fee deficiencies or additional fees are payable, please charge the same or credit any overpayment to our Deposit Account (Account No. 04-0213).

Respectfully submitted,

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